



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

10/660,115

09/10/2003

Jonathan Axon

219002029400

6854

25225 7590 12/28/2007
MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

EXAMINER

BALASUBRAMANIAN, VENKATARAMAN

ART UNIT

PAPER NUMBER

1624

MAIL DATE

DELIVERY MODE

12/28/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/660,115

Applicant(s)

AXON ET AL.

Examiner/Venkataraman
Balasubramanian/**Art Unit**

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 September 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,4-19,21,22 and 24-27 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,4-19,21,22 and 24-27 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicants' response, which included cancellation of claims 20, 23, addition of new claims 24-27 and amendment to claim 1 and 4, filed on 9/21/2007, is made of record. Claims 1, 4-19, 21, 22 and 24-27 are now pending.

In view of applicants' response, the 112 first and second paragraph rejections made in the previous office action have been obviated. However, the following 103 rejections made in the previous office action are maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 21, 22 and 24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cai et al., WO 02/47690 for reasons of record. The rejection along with previous response to applicants' traversal is presented below:

Cai et al. teaches several pyrimidine compounds, which include compounds, composition and the method of use claimed in the instant claims. See formula I on page 10 and note when A=C, given the same pyrimidine core, all variable groups overlap with those of the instant claims. Especially see formula II and III on page 11-12 which shows the desired pyrimidine compounds. See entire document for the details of the invention.

See pages 13-34 for various species of pyrimidine compounds. Particularly, see page 22, species 13, 14, page 34, species 1, 2 for pyridylamino bearing pyrimidine species, page 23 species 1,2, page 29, species 10, page 31, species 11 for indoylamino bearing species, and see page 22, species 15, 16 17 for pyrimidinylamino bearing pyrimidine species. For benzimidazolylamino bearing species see page 33, species 16. Note all these differ from instant claims in not having a phenyl or substituted phenyl in 2-position of the pyrimidine ring. However, note in page 13 species 7, 8, page 14, species 18, 19, page 16 species 9, 11, 13, 15 and 17, Cai et al., teaches phenyl substituents in

2-position. See pages 139-152 for Table of compounds. Especially see compound 73, 75, 81, 46 and 20.

Cai et al differ from instant claims in not exemplifying 2-phenyl substituted pyridylamino, pyrimidinylamino, indoylamino and benzimidazolylamino pyrimidines, which fall in the genus of instant compounds.

However, Cai et al. teaches the equivalency of alternate choices for the groups in 2-position, 4-position and 6-position those compounds exemplified with specific substituents in pages 13-34 and in Table of pages 139-152 with those compounds generically recited on page 10-12 for Formula I-III See formula I-III and note the definition of various variable groups include several compounds.

Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make pyrimidine compounds variously substituted with Ar1, Ar2, R1, R2 and R3 as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above. More specifically, based on the species pointed out above in pages 22, 23, 29 and 31, differ only in not having a phenyl or substituted phenyl in 2-position of the pyrimidine ring and based on the teaching of phenyl substituents in 2-position in species pointed out in pages 13, 14 and 16, one trained in the art would be motivated to make compounds with 2-phenyl substituents along with 4-pyridyl amino, 4-indoylamino, 4-pyrimidinylamino and 4-benzimidazolylamino groups in the pyrimidine ring and expect these compounds to have the same use recited therein.

This rejection is same as made in the previous office action but now includes further explanation of the basis for the rejection. As shown above, the species pointed out differ in one variable only. That is, there is guidance in the reference to make compounds which will differ from the instant compound of formula I in only one variable group at 2-position of the pyrimidine ring. Whereas the species pointed out have pyridyl group at 2-position, instant claims require a phenyl in that position. Again, as pointed out reference clearly permits phenyl in position of the pyrimidine ring. Hence, contrary to applicants' urging, it would be obvious to one trained in the art that 2-phenyl substituted pyrimidines bearing pyridylamino, indoylamino, pyrimidinylamino and benzimidazolyl amino groups at the 4-position would be also have the same use taught in the reference.

As for the issue of "equivalency" the term is used in the sense alternate choices are equivalent as far as the desired activity of the genus of compounds. In other words, as much as alternate choices embraced as substituents in the pyrimidine core are assumed to have the same activity, the alternate choices set forth in the reference are given the same meaning. More specifically, instant claims embrace various variables as alternate choices of substituents in the pyrimidine and as recited in claims 20 and 23 are said to have the same utility. Likewise, alternate substituents taught in the reference for the pyrimidine core would also result in compounds with the use taught in the reference. Hence, one trained the art would be motivated make compounds with alternate choices substituents with the guidance provided in the reference and expect

these compounds have the same use taught for exemplified compounds of the reference.

Hence, this rejection is proper and is maintained.

Response to the current traversal:

This rejection is same as made in the previous office action but now excludes cancelled claims and includes newly added claims.

Applicants argued that claim 23 which relate liver fibrosis should not have been rejected. But a careful look at claim 23 as presented in amendment dated 8/15/2006, shows that claim 23 was dependent on claim 20. Claim 20 recited a method to treat fibroproliferative disorder or cancer while claim 23 recited wherein the condition is fibrosis of liver. In this context the rejection is proper and hence applied now to claims 25-27. Cai et al., teaches the mode of action of their compounds to be antiproliferative, this rejection is deemed as proper. However, applicants can show that that such is not the case and liver fibrosis is not the same as proliferative disorder as originally presented. In such case, examiner will withdraw the rejection of claims 25-27.

Applicants again have argued that examiner had not made a prime facie case for obviousness. This is again incorrect. As seen, above the rejection clearly includes teaching, suggestion and motivation and thus meets the 103 obviousness requirement.

Contrary to applicants' urging, Takeda Chem. Indus., Ltd. V. Alphapharm Pty. Ltd., is not the point. Court held that: Prima facie case of obviousness for claimed chemical compound requires showing of structural similarity between prior art compound and claimed compound, as well as showing that prior art would have

Art Unit: 1624

suggested making specific molecular changes necessary to achieve claimed invention; this test is consistent with legal principles prohibiting rigid application of “teaching, suggestion, or motivation” test in obviousness inquiry, since TSM test can provide helpful insight if it is not applied as rigid and mandatory formula, and since, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led chemist to modify known compound, in particular manner, in order to establish prima facie obviousness of new compound.

Claimed thiazolidinedione derivatives used as antidiabetic agents cannot be found obvious over closest prior art compound, identified as “compound b,” under “obvious to try” standard, since that standard is applicable if prior art contains finite number of identified, predictable solutions, whereas prior art in present case, rather than identifying predictable solutions for antidiabetic treatment, disclosed broad selection of compounds, any one of which could have been selected as “lead compound” for further investigation, and since compound b exhibited negative properties that would have directed person of ordinary skill in art away from that compound; nothing in prior art provided motivation to narrow possibilities for lead compound to compound, since evidence supports finding that one of ordinary skill would have chosen as starting point one of more than 90 compounds in prior art that did not disclose existence of toxicity or side effects, rather than compound with identified adverse effects.

Such is not the case in the instant situation. Cai et al., teaches that Ar₁ and Ar₂ are independently and optionally substituted aryl and then provides preferred choices of Ar₁ and Ar₂ which include phenyl, pyridyl and indoyl as shown in page 11. Cai et al

also teaches several species in pages 13-34. These include phenyl in the 2-position of the pyrimidine, pyridyl in 2- position of pyrimidine with variously substituted phenyl amino and indoylamino in 4- position. See page 13, 29, 31 and 34. Thus, Cai et al., provides adequate guidance for one trained in the art to choose such substituents. It is within the skill level of one trained in the art to use various Ar_1 and Ar_2 at 2 and 4 position of the pyrimidine given the guidance and showing that such compounds would have desired use.

As for applicants' arguments citing *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007), all the TSM requirement is clearly met with as seen above. Furthermore, the court stated that

[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Such is the case with instant situation. Cai et al., teaches generically a finite number of choices for Ar_1 and Ar_2 and exemplifies such choices with several species. One trained in the art would be motivated to make various Ar_1 and Ar_2 choices including the instant choices and expect the analog to have the same use as taught for the exemplified cyclic analog.

Hence, based on these considerations, this rejection is proper and is maintained.

Claims 1, 4-16, 18, 19, 22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kleemann et al., US 5,849,758 for reasons of record. The rejection along with previous response to applicants' traversal is presented below:

Kleemann et al. teaches several pyrimidine compounds, which include compounds claimed in the instant claims. See formula I on column 1 and note when Z is N, given the same pyrimidine core, and A is aryl or heteroaryl, compounds taught by Kleemann et al include those of the instant claims. See column 1-3 for the details of the invention. See column 3-5 for various species of pyrimidine compounds. See Table X for various compounds, which include instant compounds.

Kleemann et al, although exemplifying several compounds, which fall in the genus of instant compounds, does not fully exemplify all compounds embraced in the genus of Formula I. However, Kleemann et al. teaches the equivalency of those compounds exemplified with specific substituents with that generically recited for formula I. See formula I and note the definition of various variable groups include several compounds. Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make variously substituted pyrimidine compounds as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

This rejection is also same as made in the previous office action but now limited currently pending claims. Applicants' argument to overcome this rejection is not persuasive.

Applicants argued that alternate choices are not equivalent. That is according applicants, although Kleeman et al., teaches compounds of formula I wherein $X=O$, which anticipated instant compounds and was obviated by excluding $X=O$, teaching of Kleeman et al., would only limited to exemplified compounds not other alternate choices. This is not persuasive.

First of all, Kleeman permits $X=O$ and $X=S$ as much as applicants are permitting $X=NR$ and $X=S$ in currently pending claims. It should be pointed out the original claims had $X=O$ as well. Therefore alternate choices should be given equal weight whether it is instant application or a reference.

Secondly, applicants argued that since $X=S$ compounds are not exemplified and Kleeman et al., gets good results with $X=O$ compounds, the reference is limited $X=O$ teaching only. This is again not persuasive. There is no explicit teaching or statement in Kleeman et al., to indicate the $X=S$ compounds are inactive. Applicants have not provide d any such evidence.

Thirdly, applicants have not made any compound of instant claims wherein $X=S$ but relies on compounds wherein $X=O$ to assert activity.

Finally, as for legal standard, note In re Bruckel which states “References must be considered under 35 U.S.C 103, not only for what it expressly teaches but also for what it fairly suggests; all disclosures of prior art, including unpreferred embodiments must be considered in determining obviousness”. In re Bruckel, 201 USPQ 67.

The equivalency teaching of alternate choices of $X=O$ with $X=S$, should therefore be given due consideration as much as instant Markush choices of X mentioned above.

This rejection is proper and is maintained.

Response to the current traversal:

This rejection is same as made in the previous office action but now excludes cancelled claims and includes newly added claim 24.

Applicants' traversal is more or less same as before except citing the above two case laws. Again Contrary to applicants' urging, Takeda Chem. Indus., Ltd. V. Alphapharm Pty. Ltd., is not the point. Based on the teaching of Kleeman, one trained in the art would expect that both $X=O$ and $X=S$ compounds would share the same taught therein and it is with the skill level of one trained in the art to grasp that alternate choices for X would be have same utility. Unlike the cited case law, the teaching of $X=O$ compounds and their use would provide guidance and motivation to make and use the compounds where $X=O$.

As for applicants' arguments citing KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727 (2007), all the TSM requirement is clearly met with as seen above. Furthermore, the court stated that

[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads

to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Thus, substituting X=S for X=O in compounds taught by Kleeman is of ordinary skill.

Hence, based on these considerations, this rejection is proper and is maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any

Art Unit: 1624

inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

/Venkataraman Balasubramanian/

Primary Examiner, Art Unit 1624

12/26/2007